IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	EXAMINER: E. WEBMAN
CATANIA ET AL.	ART UNIT: 1502
SERIAL NO.: 08/328,977	
FILED: OCTOBER 24, 1994	
FOR: TASTE-MASKING COMPOSITION OF BITTER PHARMACEUTICAL AGENTS	

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 C.F.R. §1.132

I, William J. Curatolo, do hereby declare as follows:

1. I received a Bachelor of Engineering in Electrical Engineering from Manhattan College, a Master of Arts in Biology from the State University of New York at Binghamton, and a Doctor of Philosophy degree in Biochemistry/Biophysics from Boston University. I was a Postdoctoral Fellow in the Departments of Biology and Chemistry at the Massachusetts Institute of Technology from 1977-1979. I was a Staff Scientist in the Molecular Biophysics Section in the Francis Bitter National magnet laboratory at the Massachusetts Institute of Technology from 1979-1983. I have worked for twelve years in the Pharmaceutical Research and Development Department at Pfizer Central Research as a drug formulator and manager of drug formulators. I am currently an Assistant Director with responsibility for oral drug delivery, controlled release dosage forms and biopharmaceutics. I am an elected Fellow of the American Association of Pharmaceutical Scientists. The designation "Fellow" recognizes exceptional technical expertise in Pharmaceutics and Drug Delivery.

2. I have reviewed and am familiar with the above-identified patent application, U.S. Serial No. 08/328,977 ("the '977 application"), which contains claims directed to taste-masked formulations of azalide antibiotics and particularly of azithromycin. The '977 application claims compositions of azalides which are taste-masked by the use of an alkaline earth oxide. The '977 application also claims compositions of azalides which are taste-masked by the use of a combination of an alkaline earth oxide and an aldonic acid. In particular, the invention is directed to the use of magnesium oxide as the alkaline earth oxide and calcium gluconate as the aldonic acid.

3. Azithromycin is an azalide antibiotic with chemical, physical, biological and pharmaceutical properties quite different from other antibiotics, including erythromycin. Further, azithromycin is 326 times more stable than erythromycin in solution (Fiese and Steffen, Journal of Antimicrobial Chemotherapy, 1990, 25, Suppl. A, 39-47, a copy of which is attached as Exhibit A). Azithromycin differs structurally from erythromycin by having a 15-membered ring rather than a 14-membered ring. Further, azithromycin lacks the C-9 ketone of erythromycin, having instead a (methyl)amino methylene group between the C-8 and C-10 carbons. As a result of its unique chemical structure, azithromycin has an exceptionally long elimination half-life (69 hours in humans), which permits successful therapy with once-daily dosing for one to five days. By contrast, erythromycin has an approximately two hour elimination half-life in humans, and must be dosed multiple times per day for many days. These elimination half-life distinctions reflect different sensitivities to metabolic enzymes in the human body, and are also reflective of differences in the chemical labilities of these two distinct antibiotics. Azithromycin is also chemically stable in the solid state. Thus, there is no need to stabilize azithromycin.

4. I have reviewed U.S. Patent 3,627,885 ("Rondelet"), which discloses granulations of chemically unstable antibiotics for use in mixing into animal feed. Rondelet discloses a wide variety of antibiotics which can be stabilized according to the invention claimed therein. The most closely related structure to azithromycin disclosed therein is erythromycin. Azalide antibiotics, including azithromycin, are not included. Since azithromycin is intrinsically chemically stable as stated above, there is no reason to improve the chemical stability by adding an alkaline earth oxide as taught by Rondelet. Therefore, one of ordinary skill in the art would not be motivated to use the teachings of Rondelet when attempting to taste mask azithromycin.

5. The field of art of the Rondelet patent is animal feeds and in particular is directed to the stabilization of drugs prone to chemical degradation. A worker of ordinary skill in the art of human drug formulation would not generally be aware of any publications or other knowledge in the area of stabilization of drugs against chemical degradation in animal feeds. The properties of a drug which relate to a propensity toward chemical degradation in an animal feed (or even in human formulations) are unrelated to the properties of a drug which determine the taste of a drug. For example, propensity toward chemical degradation is related to the lability of specific covalent chemical bonds in the compound whereas taste is related to the three-dimensional organization of various chemical groups in the molecule and how this organization relates to the structure of taste receptors on the tongue. Therefore, the literature relating to methods of stabilizing antibiotics contained in animal feeds hold no interest for a person in the art of taste-masking since said literature would not be expected to discuss taste-masking. Further, even if a person in the area of taste-masking were aware of Rondelet, the disclosure therein would not be applied to azithromycin because there is no need to stabilize azithromycin.

6. I have reviewed U.S. Patent No. 4,678,661 ("Gergely"), which discloses the use of calcium gluconate to maintain the dryness of an effervescent formulation. Gergely relates to effervescent formulations which are reconstituted by mixing with water. The disclosure in Gergely is directed only to the maintenance of the effervescent property of the formulations taught therein. Gergely does not disclose taste-masking. It would be highly unusual to consider adding a drying agent to a non-effervescent formulation such as any of the formulations exemplified in the '977 application. Therefore, a person working on a taste-masking problem would not be motivated to search the art in the area of effervescent formulations for a solution to a taste-masking problem. In fact, in my entire experience as a formulation chemist, I have never considered the use of effervescent formulations and am entirely unfamiliar with the field of art relating to effervescent formulations of pharmaceutical agents.

7. I have also reviewed U.S. Patent No. 4,761,274 ("Denick"), which discloses the adsorption of a solution of a drug onto a solid complex magnesium aluminum silicate sorbent which contains magnesium oxide in addition to at least six other components. Denick describes (column 4, lines 51-52) "sorbing the medicament drug <u>within</u> the complex magnesium aluminum silicate..." (emphasis provided). It is clear that Denick discloses sorption of a small amount of drug (in solution) into a large excess of magnesium aluminum silicate. In the '977 application, a solution of the drug is not adsorbed onto a sorbent. The solid azalide is mixed with

a smaller amount of solid magnesium oxide (see Examples 1-15 of the '977 application). While the '977 application does not set forth a mechanism for the taste-masking effect of magnesium oxide, the mechanism does not involve the encapsulation, even transiently, of the azithromycin. In fact, page two of the '977 specification clearly states that encapsulation suffers from disadvantages which it is the purpose of the '977 application to correct. Denick, on the other hand, achieves taste-masking because the magnesium aluminum silicate **encapsulates** the drug, thus transiently protecting it from dissolution in the mouth. Consideration of the disclosure of Denick would not lead one of ordinary skill in the art to simply prepare a dry blend of azithromycin or any azalide with a smaller quantity of magnesium oxide. In fact, Denick's disclosure actually teaches away from both dry blending and from the use of alkaline earth oxides in amounts smaller than the amount of the drug.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 8/21/95

William J. Curatolo

WILLIAM J. CURATOLO

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Comparison of the acid stability of azithromycin and erythromycin A

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In acidic aqueous media, erythromycin A is rapidly degraded via intramolecular dehydration to form erythromycin-6,9-hemiketal and then anhydroerythromycin, both of which possess little antimicrobial activity. Azithromycin, a new azalide antibiotic, has a methyl-substituted nitrogen in place of the carbonyl at the 9a position of the aglycone ring, thus blocking the internal dehydration pathway. As a result, azithromycin decomposition occurs primarily via acid-catalysed hydrolysis of the ether bond to the neutral cladinose sugar.

Rate constants and the time for 10% decay ($T_{1,10}$) were determined for both azithromycin and erythromycin A at pH 2 using various levels of acetonitrile cosolvent and constant ionic strength. Semi-log plots of the decay rate constants versus the reciprocal of the solution dielectric constants were used to extrapolate to totally aqueous conditions. In solution at 37°C and pH 2 with ionic strength $\mu = 0.02$, azithromycin was degraded with a $T_{1,10}$ of 20·1 min while erythromycin underwent 10% decay in only 3·7 sec. The activation energy for hydrolysis of the ether bond connecting cladinose to azithromycin was 25·3 kcal/mol while the internal dehydration reaction of erythromycin had an activation energy of 15·6 kcal/mol.

A solution stability profile was generated for azithromycin over the pH range of 1·0 to 4·1 at 30°C. Stability was found to improve ten-fold for each unit increase in pH.

Introduction

In aqueous acidic media, erythromycin is known to undergo rapid decomposition via the pathway shown in Figure 1. The rate limiting first step of this reaction is reported to be subject to both general and specific acid catalysis with a stability maximum in the range of pH 7·5 to 8·5 (Kondrat'eva & Bruns, 1962; Kurath *et al.*, 1971; Amer & Takla, 1978; Atkins, Herbert & Jones, 1986). This decomposition reaction is also catalysed by cupric, ferrous and aluminium cations (Amer & Takla, 1978). Both the 6,9-hemiketal and anhydroerythromycin are known to be inactive against Gram-positive bacteria normally affected by erythromycin (Stephens & Conine, 1959).

Azithromycin (CP-62,993, XZ-450), the prototype azalide antibiotic, differs structurally from erythromycin A by replacing the 9a carbonyl in the aglycone ring with a methyl substituted nitrogen, as well as expansion of the ring to 15 members (Bright *et al.*, 1988). This structural difference blocks the internal reaction to form the hemiketal, leaving acid hydrolysis of the ether bond to the neutral cladinose sugar as the main decomposition pathway (Figure 2). Data from the erythromycin literature suggest that the azithromycin decay product without the cladinose sugar, CP-66,458, will lack bioactivity (LeMahieu *et al.*, 1974; Kibwage *et al.*, 1987).

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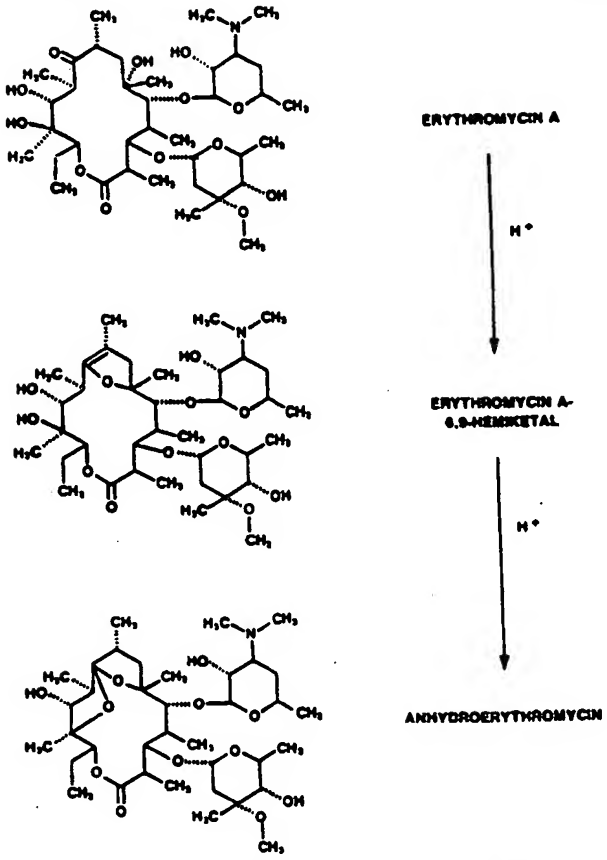

Figure 1. Decomposition pathway for erythromycin in aqueous acidic medium.

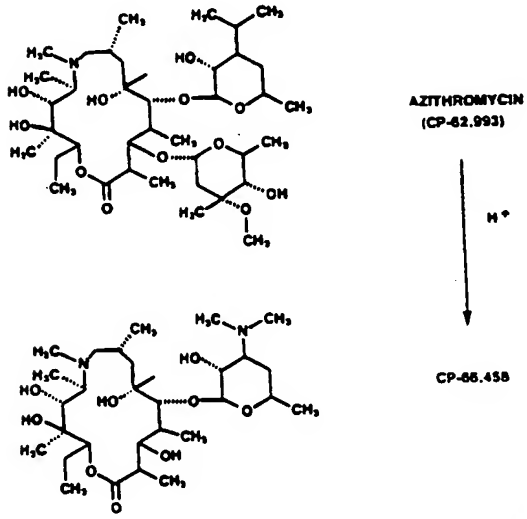

Figure 2. Decomposition pathway for the azalide, azithromycin, in aqueous acidic medium.

The objective of this study was to examine the stability of azithromycin in acidic solution and compare this with erythromycin stability.

Materials and methods

Antibiotics

Azithromycin was prepared at Pfizer Central Research, Groton, CT. Erythromycin A was obtained from The Upjohn Company, Kalamazoo, MI. Oleandomycin was obtained from Pfizer Taito Co. Ltd, Nagoya, Japan. All degradation products were isolated on site and identification was verified by NMR and mass spectroscopy, using published values (Kurath & Egan, 1971; Kurath *et al.*, 1971; Kibwage *et al.*, 1987; Bright *et al.*, 1988).

HPLC assay

A reverse-phase HPLC assay was developed for each antibiotic using an alkaline mobile phase and a polystyrene divinylbenzene stationary phase (Table I). The equipment for this assay consisted of a M6000A pump and a Model 441 detector, λ = 214 nm, (Waters Chromatography Division, Millipore Corporation, Milford, MA), a PRP-1 analytical column, 5 μ, 4·1 mm ID × 15 cm L (Hamilton Company, Reno, NV), and a HP3390A integrator (Hewlett Packard Co., Avondale, PA). The temperature of the column was maintained at 50°C with a Model 725-1010 column heater (Rainin Instrument Co., Woburn, MA). The flow rate was maintained at 1 ml/min. The injection volume was 50 μl. All reagents in these assays were used as received (Fisher Scientific and Sigma Chemical Co.) without further purification.

These HPLC assays were derived by slight modifications of several published assays for erythromycin (Kibwage *et al.*, 1985; Nilsson, Walldorf & Paulsen, 1987). In each case, the intact parent compound was clearly separated from the decay products, so that consecutive reaction products could be monitored if necessary. The sensitivity of the assay for each compound was 10 mg/l and linear responses were obtained up to 2 g/l.

Table I. Reverse-phase HPLC assay conditions used to study the acid decay of erythromycin A and azithromycin

Mobile phase: (% v/v)	
erythromycin A	azithromycin
20·0% TRIS 0·02 M	10% TRIS 0·02 M
27·5% TBAOH 0·02 M	20% TBAOH 0·02 M
52·5% Acetonitrile	10% Isopropanol
	60% Acetonitrile

Each mobile phase was adjusted to a final pH10 with concentrated phosphoric acid.

TRIS, tromethamine; TBAOH, tetrabutylammonium hydroxide, 40% solution.

Methods

Aqueous buffers for this study consisted primarily of 0·01 N HCl (pH 2) with sufficient NaCl to bring all the buffers to constant ionic strength (μ = 0·02). Buffers at higher pH values were prepared from mixtures of 0·01 M citric acid and 0·02 M sodium phosphate with the ionic strength adjusted to μ = 0·02 with NaCl.

Since the decay of erythromycin at pH 2 is known to be very rapid, a stock solution in acetonitrile was used to give a precise kinetic time zero at the time of drug addition. Portions of acetonitrile (5–25% v/v) were pre-mixed with the buffers to eliminate thermal changes due to heat of mixing upon addition of the stock antibiotic solution. Acetonitrile was chosen for the cosolvent because of its known linear change in solution polarity with changing cosolvent levels (Cunningham, Vidulich & Kay, 1967).

Before each experiment, the aqueous buffers and stock solutions of antibiotic in acetonitrile were pre-equilibrated at the desired temperature. At time zero, 10 ml of the stock antibiotic solution was added to 90 ml of buffer solution which was being mixed vigorously. This addition of acetonitrile stock drug solution brought the final solution to 15, 25 or 33·3% v/v cosolvent. After the antibiotic was added to the buffer, samples were withdrawn at various times, neutralized with an equal volume of mobile phase and then quantitatively assayed by HPLC. The erythromycin studies used acid stable oleandomycin as an internal marker to correct for mass balance during the rapid neutralization step (Nilsson *et al.*, 1987).

In all cases, first order decay kinetics were observed and monitored through at least two half-lives. Decay rate constants (k) were determined by linear regression analysis and the time for ten percent decomposition ($T_{1/10}$) calculated from these decay rates. To construct a pH stability profile, a solution of pH 1 was prepared using 0·1 N HCl which had an ionic strength of μ = 0·105 without addition of NaCl, a higher ionic strength than solutions at pH 2–4. For neutralization of samples from this acidic buffer, three parts of neutralization medium, consisting of 66% v/v acetonitrile and 34% 0·2 M tromethamine, were mixed with one part of sample.

Results

Erythromycin A

Figure 3 shows the effect of acetonitrile cosolvent, plotted as the reciprocal of the solution dielectric (ε) constant, on the decay of erythromycin A at pH 2 and at three temperatures. The lower values on the x-axis ($1/\varepsilon$) correspond to higher levels of cosolvent. Extrapolation of the line of best fit obtained by linear regression to the dielectric constant for water of 78·35 ($1/\varepsilon$ = 0·0127) gave rate constants and $T_{1/10}$

Table II. First order decay rate constants and $T_{1/10}$ values for erythromycin A at pH 2 and ionic strength μ=0·02 in the absence of acetonitrile cosolvent

Temperature (°C)	k (min^{-1})	$T_{1/10}$ (min)
30	0·94	0·1120 (6·72 sec)
40	2·29	0·0460 (2·76 sec)
50	4·67	0·0226 (1·36 sec)

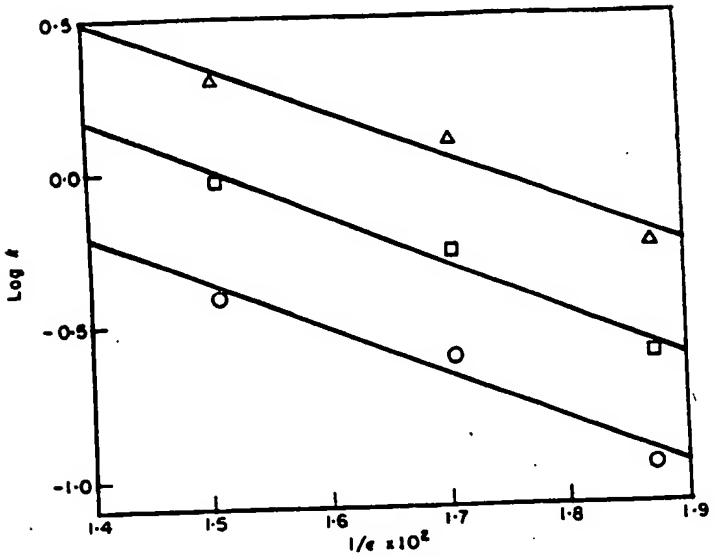

Figure 3. Effect of temperature and acetonitrile cosolvent level on erythromycin decay rate constants (k) in aqueous acidic (pH 2) media. △, 50°C; □, 40°C; ○, 30°C.

values for a totally aqueous medium (Table II). The presence of the internal marker oleandomycin did not alter the observed decay kinetics. Figure 4 shows an Arrhenius plot of temperature versus decay rate constants which, when analysed by linear regression, gave an activation energy of 15·6 kcal/mol. From Figure 4. $T_{1/10}$ was determined to be 0·0616 min (3·7 sec) for acid decay of erythromycin A at 37°C.

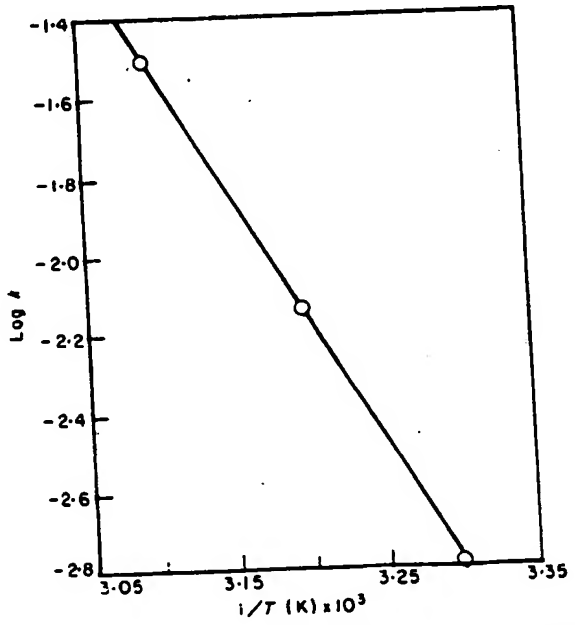

Figure 4. Arrhenius plot of temperature versus first order decay of erythromycin A at pH 2. E_{act} = 15·6 kcal.mol.

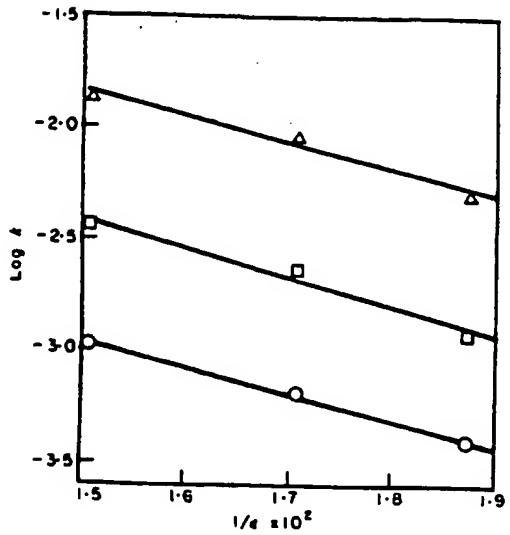

Figure 5. Effect of temperature and acetonitrile cosolvent on azithromycin decay rate constants in aqueous acidic (pH 2) media. △, 50°C; □, 40°C; ○, 30°C.

Azithromycin

Figure 5 shows the effect of cosolvent on the acidic decay of azithromycin at three temperatures. The decay rate constants and $T_{1/10}$ values were determined by extrapolating to a totally aqueous environment (Table III). As azithromycin was relatively stable in this acidic medium, a similar set of decomposition reactions was conducted in media without acetonitrile cosolvent and the results are shown as 'actual' data.

An Arrhenius plot of temperature versus first order decay rate constant data for azithromycin gave an activation energy of 25·3 kcal/mol (Figure 6). The $T_{1/10}$ of azithromycin at 37°C was 20·1 min. Similar results were obtained for acidic (pH 2, 37°C) hydrolytic cleavage of cladinose from anhydroerythromycin (activation energy = 28·8 kcal/mol: $T_{1/10}$ = 16·7 min).

Figure 7 shows an expanded pH-stability profile for azithromycin at 30°C in the absence of cosolvent. Although most of these data were generated with solutions at constant ionic strength (μ = 0·02), the highly acidic solution at pH 1 also had a higher ionic strength, μ = 0·105. The data in Figure 7 indicate a ten-fold increase in stability for each unit increase in pH.

Table III. First order decay rate constants and $T_{1/10}$ values for azithromycin at pH2 and ionic strength μ=0·02 and in the absence of acetonitrile cosolvent

Temperature (°C)	Extrapolated data k (min^{-1})	Extrapolated data $T_{1/10}$ (min)	Actual $T_{1/10}$ (min)
30	2·028 × 10^{-2}	51·96	64·9
40	7·787 × 10^{-2}	13·53	14·5
50	2·726 × 10^{-1}	3·87	3·34

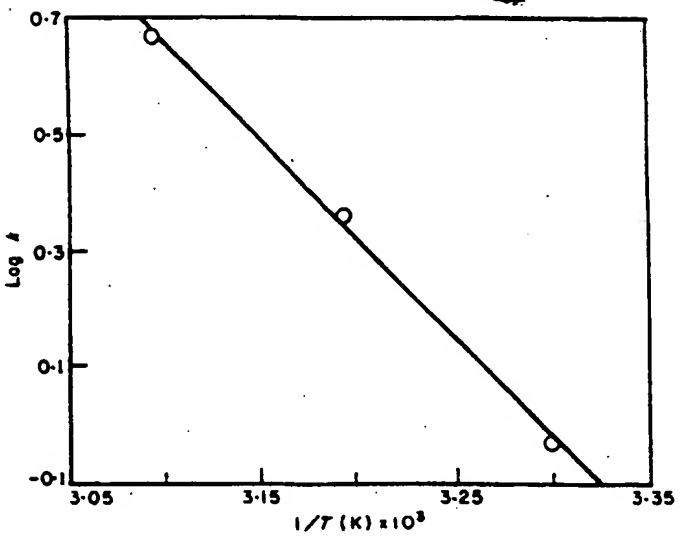

Figure 6. Arrhenius plot of temperature versus first order decay of azithromycin at pH 2. E_{as} = 25·3 kcal/mol.

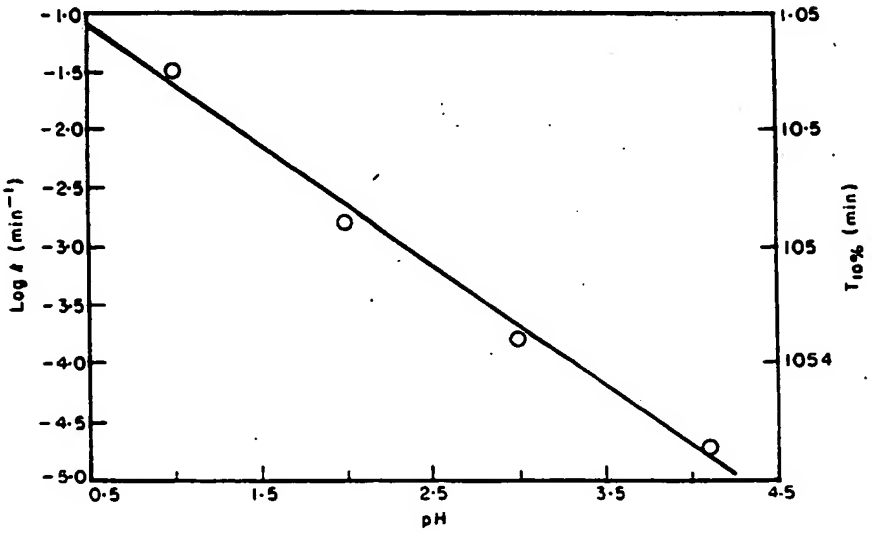

Figure 7. pH-stability profile for azithromycin at 30°C in the absence of cosolvent.

Discussion

Kondrat'eva & Bruns (1962) generated an exponential equation to describe the pH stability profile for erythromycin from pH 3 to 12 and from 0 to 70°C in media without acetonitrile cosolvent. This equation was used to compute the kinetics for decay at 37°C and pH 2, resulting in a $T_{1\,10}$ prediction of 3·3 sec with an activation energy of 19·1 kcal/mol. These values are close to the values observed in the present study ($T_{1\,10}$ = 3·7 sec and activation energy = 15·6 kcal/mol).

A reduction in the reaction rates with increasing acetonitrile cosolvent level is consistent with formation of a solvent shield around the attacking proton (Laidler, 1965). Further proof of this mechanism will require additional studies with cosolvents varying in dielectric constant and molecular size.

The acid-catalysed hydrolysis of the ether bond connecting the 15-member aglycone ring of azithromycin to the neutral cladinose sugar is consistant with published information concerning ether bonds (Burwell, 1954). The mechanism proposed for this reaction starts with proton attack on the ether oxygen followed by cleavage to the respective alcohols. The effect of cosolvent on creating a solvent shield around the attacking proton could account for the observed decrease in decay rate with increasing cosolvent level. In addition, a linear pH-stability profile in which each unit change in pH results in a ten-fold change in decay rate (Figure 7) is consistent with this mechanism. As expected, the acid decay product was found to have no in-vitro activity against micro-organisms normally sensitive to erythromycin and azithromycin (Girard, A. E., personal communication).

The pharmaceutical significance of this study lies in the difference in the chemical stability of the two antibiotics in media similar to gastric fluid. The acid instability of erythromycin requires enteric formulations that protect the antibiotic from stomach acidity. As macrolides are thought to be absorbed primarily in the upper duodenum, the enteric polymer coating must protect the compound in the stomach, but then dissolve quickly at pH 4–5 to deliver the drug to the site of maximum absorption (Watanabe *et al.*, 1978). The inherent acid stability of azithromycin suggests that an enteric formulation may not be necessary. The greater acid stability of azithromycin may account for higher plasma concentrations than are obtained with oral erythromycin (Girard *et al.*, 1987).

Acknowledgements

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Nomenclature and the PLURONIC® Surfactant Grid

The PLURONIC® Surfactant Grid is a graphic presentation of the PLURONIC surfactant series. Plotting molecular weight ranges of the hydrophobe (propylene oxide) against the weight-percent of the hydrophile (ethylene oxide) present in each molecule allows property trends of the product structure to be analyzed on the Grid. The Grid also clarifies the use of the letter-number combinations to identify the various products of the PLURONIC series. The alphabetical designation explains the physical form of the product: 'L' for liquids, 'P' for pastes, 'F' for solid forms. The first digit (two digits in a three-digit number) in the numerical designation, multiplied by 300, indicates the approximate molecular weight of the hydrophobe (vertical axis at the left of the Grid). The last digit, when multiplied by 10, indicates the approximate ethylene oxide content in the molecule, read from the horizontal axis.

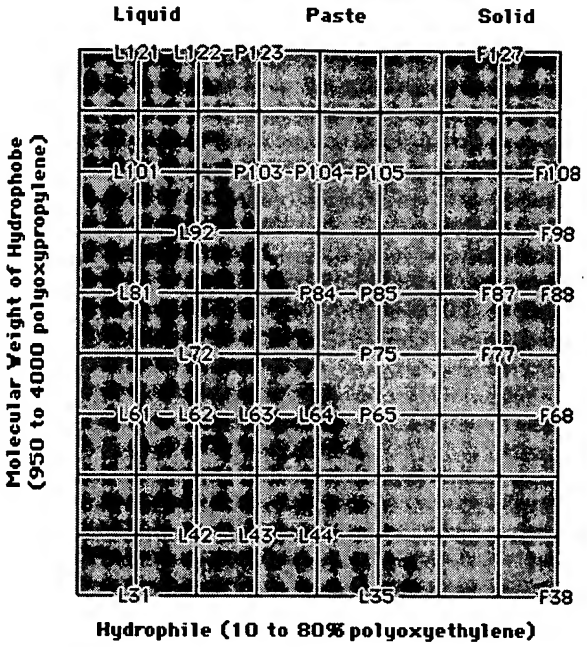
For example, from the Grid, we immediately learn that PLURONIC F 68 is a solid material. The molecular weight of the hydrophobe is approximately 1800 (6 X 300). The hydrophile represents approximately 80% of the molecule, by weight, (8 X 10).

The PLURONIC® R Surfactant Grid also shows the relationship between the hydrophobe and hydrophile of each product. Again, hydrophobe molecular weight is plotted against weight percent hydrophile. The letter 'R' found in the middle of each designation signifies that this product has a reverse structure compared to the PLURONIC products, i.e., the ethylene oxide (EO) hydrophile is sandwiched between the propylene oxide (PO) blocks. The numeric designation preceding the 'R', when multiplied by 100, indicates the approximate molecular weight of the PO block. The number following the 'R', when multiplied by 10, indicates the approximate weight percent EO in that product.

So from the Grid, we immediately learn that 25R4 contains 40% EO (4x10) and the approximate molecular weight of the combined PO blocks is 2500 (25x100).

PLURONIC | PLURONIC R

Basic Grid | Best Defoaming | Best Detergency | Best Foaming | Best Emulsification | Best Gel Formation | Best Wetting



The Basic PLURONIC Grid

This grid represents the relationship between copolymer structure, physical form and surfactant characteristics by plotting molecular weight ranges of the hydrophobe against the percent of hydrophile in the final molecule.

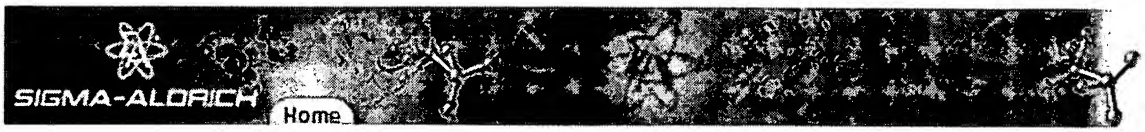
The structure of each grade shown on the grid is defined by the intersection of the hydrophobe molecular weight and the percent hydrophile.

The grids describe the degree of variation that has been achieved in the laboratory. Many of the products described are currently available from prouction sites located in Washington, NJ, and Whitestone, SC.

To see a property profile of any PLURONIC grade, click on the intersection where the grade is identified.

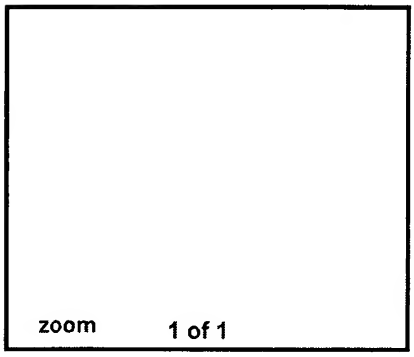
What function do you want your formulation to perform? Select any of the six functions from the tabs above. The interactive BASF PLURONIC Grid changes to display a region containing those PLURONIC surfactants best suited to the function chosen.

Nomenclature and the PLURONIC Grid | Storage and Handling



81113 Synperonic PE®/L61

Fluka **liquid phase for GC, block copolymer of polyethylene and polypropylene glyc**



Synonym	Pluronic® L61 Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) Poly(propylene glycol)-*block*-poly(ethylene glycol)-*block*-poly(propylene glycol)
CAS Number	9003-11-6
EG/EC Number	EINECS
MDL number	MFCD00082049

Expand/Collapse All

Price and Availability

Click For Pricing and Availability

Properties

grade	liquid phase for GC
mol wt	mol wt <2000
density	1.02 g/mL at 20 °C

References

Merck	*Merck* **13**,7644
reference	*FT-IR2* **2** (3), 4673:D / *Structure Index* **1**, 498:A:7

Safety

Safety Statements	23-24/25
WGK Germany	2
RTECS	MD0911050

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